REMARKS

This Amendment is in response to the Office Action, dated May 19, 2008 ("Office Action"). It is respectfully submitted that the application is in condition for allowance. Claims 1-28 are pending. Claims 10-12 have been amended; claims 1-9 and 20-28 have been canceled; and claims 29-33 have been added by virtue of the present amendment. Support for these claim amendments and new claims can be found throughout the specification. No new matter has been added. Allowance and reconsideration of the application in view of Applicants' amendment and the ensuing remarks are respectfully requested.

Claim 10 has been amended to recite that the method is to treat a "cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis," to recite that the NSAID "modulates PPAR-gamma pathway," and to recite that the method is "to treat the cancer." Support for this amendment may be found throughout the specification; for example, page 5, lines 19-21.

Claims 11-12 have been amended remove "derivatives thereof, analogs thereof, pharmaceutical equivalents thereof," from the Markush groups.

New claims 29 and 30 have been added to recite particular cancers treated by the claimed method. Support for this amendment may be found throughout the specification; for example, page 9, lines 20-23.

New claims 31-33 have been added and are similar to the existing claims and focus on the use of 2C4 and R-etodolac to treat prostate cancer.

In the Office Action, the Examiner acknowledged Applicants' election of Group II (claims 10-19) and withdrew claims 1-9 and 20-28. The Examiner has determined that none of the non-elected claims are generic or linking claims. Furthermore, while acknowledging Applicants' traversal, the Examiner deemed the restriction requirement to be proper and final.

The Examiner confirmed that Applicants' Information Disclosure Statement, filed on February 20, 2008, was considered. Applicants thank the Examiner for returning an initialled copy of the PTO/SB/08a Form.

The Examiner acknowledged Applicants' claim of priority, under 35 U.S.C. §§ 371 and 119(e), to International Application No. PCT/US04/28071, filed on August 27, 2004, which in turn claims priority to U.S. Provisional Application No. 60/568,910, filed May 7, 2004, and U.S. Provisional Application No. 60/498,849, filed August 29, 2003. However, the Examiner contended that claims 10-19 do not properly benefit priority under 35 U.S.C. 119(e) and/or 120.

The Examiner argued that "the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of first paragraph of 35 U.S.C. 112," citing Transco Products, Inc. v. Performance Contracting, Inc., 38 F. 3d 551 (Fed. Cir. 1994); M.P.E.P. §201.11. The Examiner further argued that the provisional applictions did not adequately describe the claimed invention to provide written basis for the language of the present claims. As an example, the Examiner noted that the provisional application did not include "a description of treating a condition by administereing a NSAID and HER2-kinase axis inhibitor on a periodic basis," describe a combination therapy to include "gefitinib or trastuzumab," administering the agent sublingually, or administering the agents in specific ranges recited in the claims. The Examiner concluded that the effective filing date of the claims is deemed November 8, 2006, the filing date of the instant application.

Applicants respectfully traverse this finding. First, the present application is a national phase filing under 35 U.S.C. §365 of PCT/US04/28071, which was filed on August 27, 2004. There are no changes to the specification or the claims from the PCT application and thus, under §365(a), the present appliction must be afforded the August 27, 2004 filing date, at the very least.

As for the provisional applications, Ser. No. 60/498,849, filed August 29, 2003, contains claims directed to a method of treating a cancer and has disclosures that the combination treatment can increase sensitivity of epithelial cancers (*see* page 1, last

sentence). One of skill in the art would know that HER kinases are frequently upregulated in solid epithelial tumors (*e.g.*, prostate, lung, breast, glioblastoma) and the HER-kinase signaling network is known to contribute to the progression of cancer. (See *e.g.*, Agus *et al.*, *Phase I Clinical Study of Pertuzumab, a Novel HER Dimerization Inhibitor, in Patients with Advanced Cancer*. April 2005; J. OF CLINICAL ONCOLOGY 23(11):2534-2543, particularly page 2534, citing previously published studies regarding the role of HER-kinase axis and the epithelial cancers; Exhibit A.) Thus, claims 13 and 14, as amended through dependency on claim 10, have sufficient written description to be afforded priority to the provisional applications, as well as new claims 29-31 and thus must be afforded a priority date of August 29, 2003.

The specification was objected to as containing improperly demarcated trademarks. As an example, the Examiner directed Applicants' attention to page 25, line 10 of the specification, wherein the term FuGene appears. Accordingly, Applicants have made amendments the specification, shown in the "Amendments to the Specification" section above, to appropriately identify trademarks noted therein. As such, Applicants request withdrawal of this objection.

Claims 10-19 are rejected under §112, second paragraph, as allegedly being indefinite. First, the Examiner found that the term "condition," renders the claim indefinite. The Examiner asserted that the specification discloses that the invention is directed at treating and preventing disease conditions that are modulated by the PPARγ pathway and HER-kinase axis, such as cancer. The Examiner cites Dorland's Illustrated Medical Dictionary and notes that it is not evident that "cancer" is necessarily used to describe a disease that is modulated by the PPARγ pathway and HER-kinase axis. Thus, it is not evident how cancer can be regarded as representative of the conditions treated using the claimed inventive method. Second, the Examiner also found it to be unclear which agents are encompassed by the phrase "HER**2**-kinase axis inhibitors" (emphasis added). The Examiner asserted that there is no common feature/function among the inhibitors given as examples in the specification. Applicants respectfully traverse this rejection.

First, there is nothing inherently wrong with providing functional limitations in the claims. "Functional language does not, in and of itself, render a claim improper." MPEP §2173.05(g) (citing *In re* Swinehart, 439 F.2d 210, 169 USPQ 226 (CCPA 1971)). A functional limitation must be evaluated and considered for what it conveys to one of ordinary skill in the art in the context that it is used. MPEP §2173.05(g).

Second, claim 10 has been amended to recite that the method is to treat a cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis in a mammal. As the Examiner noted, the specification states that the inventive method is directed to treating a condition that is modulated by the HER-kinase axis pathway. As such, Applicants submit that the condition being treated is not indefinite.

Third, Applicants submit that one of skill in the art would recognize agents that are "HER-kinase axis inhibitors." Functional limitations are acceptable and the Examiner must evaluate and consider the functional description for what it conveys to one of ordinary skill in the art. The Examiner will find that HER-kinase axis inhibitor conveys to one of ordinary skill in the art an agent that inhibits the HER-kinase axis pathway and that these agents are well known to those of ordinary skill in the art. The Examiner argued that the inhibitors listed in claims 12 have no particular function, substantially different functions, and/or unrelated functions. Applicants submit that the Examiner is mistaken and has mischaracterized the claims. The claims call for the use of a HER-kinase axis inhibitor, which can include a HER**2**-kinase inhibitor. The listed HER-kinase axis inhibitors all inhibit the activation of the HER-kinase axis pathway, which when uninhibited is known to initiate a series of intracellular signaling events that mediate cellular proliferation and may cause cancer. (*See, e.g.*, example, figure 1 in Baselga, *A New Anti-ErbB2 strategy in the treatment of cancer: Prevention of Ligand-Dependent ErbB2 Receptor Heterodimerization*. CANCER CELL. August 2002; 2:93-95; Exhibit B.) The invention is based in part on the inhibition of the HER-kinase axis pathway and thus so long as the HER-kinase axis pathway is inhibited, regardless of the position of inhibition, one of skill in the art will recognize it as a HER-kinase axis inhibitor. Furthermore, the list of representative inhibitors provide further clarity that Applicants intend for HER-kinase axis inhibitors to include HER-kinase axis inhibitors,

regardless of the position of the inhibition in the signaling cascade. Accordingly, the term "HER-kinase axis inhibitor" does not render claims 10-19 indefinite. As such, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 10-19 are also rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner found that the terms "conditions," "HER-kinase axis inhibitor," and "NSAID" are not adequately described. The Examiner found that "condition" was not adequately described for the same reasons as noted above. Additionally, the Examiner asserts that the members of the genus "HER-kinase axis inhibitor" have different structures and/or functions, and one of skilled in the art would not be able to "envision, recognize or distinguish at least a substantial number of the different agents." Further, the Examiner first noted that NSAIDs are well known in the art, but argued that only some NSAIDs might be used effectively in combination with only some members of the genus of HER-kinase axis inhibitors to treat only some of the conditions, and concluded that the written description requirement was not satisfied for NSAIDs as well. Applicants respectfully traverse this rejection.

First, as noted above, claim 10 has been amended to recite that the method is to treat "a cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis" in a mammal. As the Examiner noted, the specification states that the inventive method is directed to treating a condition that is modulated by the HER-kinase axis pathway. As such, Applicants submit that sufficient written description is provided in the specification for the condition being treated.

Second, Applicants submit that "HER-kinase axis inhibitor" is a well known description used in the art and one of skill in the art readily is able to "envision, recognize or distinguish at least a substantial number of the different agents" that are "HER-kinase axis inhibitors." The Examiner argued that the inhibitors listed in claims 12 have no particular function, substantially different functions, and/or unrelated functions. For at least the same reasons outlined above with regard to this issue, Applicants submit that the Examiner is mistaken; that he has mischaracterized the claims; and that

one of skill in the art would readily recognize agents that are HER-kinase axis inhibitors. Thus, the written description requirement is satisfied.

Third, the Examiner admits that NSAIDs are well known in the art, but still found an alleged lack of written description because the Examiner believed that only some NSAIDs might be used effectively in combination with only some members of the genus of HER-kinase axis inhibitors to treat only some of the conditions. Applicants respectfully submit that this is not an appropriate written description rejection. NSAIDs are well known in the art and thus, the written description for NSAID is satisfied. Whether certain NSAIDS can be used with certain HER-kinase axis inhibitors is not an appropriate written description rejection. As such, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 10-19 are also rejected under 35 U.S.C. §112, first paragraph, as not being enabled. The Examiner contended that the claims are directed to unknown HER-kinase axis inhibitors and it can not be predicted whether agents can be considered HER-kinase axis inhibitors and thus, "the claimed invention cannot be used." The Examiner further alleges that "defining a substance by its principal biological activity, or its suitability for use in practicing the claimed process amounts to an alleged conception having no more specificity than that of a wish to know the identify of any material with that biological property." The Examiner also questioned whether rapamycin can be used in combination with an NSAID to treat a condition and further contended that the disclosure regarding rapamycin was only along with a disclosure of generic monoclonal antibody lacking any particular binding or special binding specificity. The Examiner determined that there does not appear to be any indication that the combination of rapamycin and any particular NSAID should be used to treat cancer and the specification provides little or no guidance aside from the disclosure that rapamycin may be considered a HER-kinase axis inhibitor. Applicants respectfully traverse this rejection.

First, as indicated above, functional descriptions can be acceptable. One of ordinary skill in the art would recognize agents that are "HER-kinase axis inhibitors" and

thus, the Examiner incorrectly alleged that the claims are directed to unknown HER-kinase axis inhibitors.

Second, the claims, as amended, are directed to treating "a cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis" by administering "an NSAID that modulates the PPAR-gamma pathway" and "a HER-kinase axis inhibitor." While in no way conceding that Examiner is correct in his analysis, the amendment to limit the condition to a cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis renders the claims commensurate in scope with the specification's disclosure. The specification discloses that HER kinases are frequently upregulated in solid epithelial tumors (*e.g.*, prostate, lung, breast, glioblastoma) and the HER-kinase signaling network is known to contribute to the progression of cancer. (*See* specification page 4, line 31 to page 5, line 4.) The role of the HER-kinase axis in epithelial tumors is well documented, as is the strong association between the HER-kinases and the aggressiveness and prognosis of solid tumors. (*See e.g.*, Agus *et al.*, *Phase I Clinical Study of Pertuzumab, a Novel HER Dimerization Inhibitor, in Patients With Advanced Cancer*. J. OF CLINICAL ONCOLOGY. April 2005; 23(11):2534-2543; Exhibit A.) The specification discloses that those who receive therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis tend to develop a resistance to their therapeutic effects after initial response to therapy. (*See* specification page 5, lines 19-21.) Based on the HER-kinase signaling cascade (see *e.g.*, Baselga, *A New Anti-ErbB2 strategy in the treatment of cancer: Prevention of Ligand-dependent ErbB2 Receptor Heterodimerization*. CANCER CELL. August 2002; 2:93-95, figure 1A; Exhibit B) and the data contained in the specification relating to prostate cancer (which is recognized by the examiner), one of skill in the art would recognize that these cancers can be treated by the claimed method. Thus, one of skill in the art would readily appreciate that a cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis is to be and can be treated by the claimed method.

Third, the claimed method is based in part upon inhibiting the HER-kinase axis pathway to overcome the resistance and treat the cancer, and thus, one of skill in the art would understand that any inhibitor of the HER-kinase axis can be beneficially used in conjunction with an NSAID that modulates the PPAR-gamma pathway.

Fourth, as for the NSAID, the claim has been amended to note that the NSAID is one that modulates the PPAR-gamma pathway. As the claimed method is based in part upon modulating the PPAR-gamma pathway to overcome the resistance, one of skill in the art would understand that any NSAID that modulates the PPAR-gamma pathway can be used in conjunction with an inhibitor of the HER-kinase axis pathway to overcome the resistance and treat the cancer.

Finally, the specification teaches and the claims claim the use of a HER-kinase axis inhibitor in conjunction with an NSAID and the specification provides examples of agents that fall under these two categories of agents. Thus, the specification indeed teaches that the use of rapamycin with any NSAID may to be used together to treat cancer. To interpret otherwise is erroneous. As such, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 10-12 are rejected under 35 U.S.C. §102(b) as being anticipated by Mitsiades *et al.* (SEMINARS IN ONCOLOGY. April 2003; 30(2):309-312). The Examiner contends that Mitsiades *et al.* anticipates claims 10-19 of the present application because Mitsiades *et al.* teaches a process of treating Waldenstrom's macroglobulinemia, by administering a quantity of a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (*e.g.*, ciglitazone or rosiglitazone) and a quantity of an ansamycin. The Examiner asserts that absent a showing of any difference, PPARγ agonists such as R-etodolac or rosiglitazone are deemed the same as NSAIDs or pharmaceutical equivalents thereof. Thus, the Examiner concluded that the treatment method disclosed by Mitsiades *et al.* anticipates the claims of the present invention. Applicants respectfully traverse this rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (MPEP

§2131 (citing Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987))).

Applicants respectfully submit that Mitsiades *et al.* does not anticipate claims 10-12. The claims call for the use of NSAIDs that modulate the PPAR-gamma pathway. The claims are also directed to a method of treating "a cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis." While ciglitazone and rosiglitazone are PPAR-gamma agonists, they are not NSAIDs. Further, Mitsiades *et al.* does not teach the treatment of a resistant cancer. Consequently, Mitsiades *et al.* does not teach each and every element of the claims and thus, does not anticipate these claims. In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §102(b).

Claims 10-19 are rejected under 35 U.S.C. §102(b) as being anticipated by Hedvat *et al.* (CANCER CELL. June 2004; 5:565-574).

The Examiner contends that Hedvat *et al.* anticipates claims 10-19 of the present application because Hedvat *et al.* teaches a process of treating prostate cancer, wherein a mammal is administered a quantity of R-etolodac and a quantity of the 2C4 antibody. Applicants respectfully traverse this rejection.

As noted above, the correct priority date for this instant application is at the very least August 27, 2004, and some claims, August 29, 2003, not November 8, 2006. Hedvat *et al.* is published in June 2004, which is not more than 1 year prior to the priority dates of the present application. Thus, Hedvat *et al.* cannot be cited as prior art under §102(b) against the present application. In light of the foregoing, Applicants request reconsideration and withdrawal of this rejection under §102(b).

Claims 15-19 are rejected under §103(a) as being unpatentable over Mitsiades *et al.* (SEMINARS IN ONCOLOGY. April 2003; 30(2):309-312). The Examiner found that as discussed *supra*, Mitsiades *et al.* teaches a process of treating Waldenstrom's macroglobulinemia. The Examiner concedes that Mitsiades *et al.* does not address a specific regimen by which the combination of the PPARγ agonist and the ansamycin

should be administered. However, Examiner asserted that it would have been obvious to one of ordinary skill in the art to optimize the effectiveness of the treatment by determining appropriate doses, schedules and routes of administration. Applicants respectfully traverse this rejection.

Two criteria that must be met to establish a prima facie case of obviousness are: (1) "there must be a reasonable expectation of success," and (2) the prior art references "must teach or suggest **all** the claim limitations." MPEP § 2142 (emphasis added).

Applicants respectfully submit that Mitsiades *et al.* does not render obvious claims 15-19. As indicated above, the claims call for the use of NSAIDs that modulate the PPAR-gamma pathway. The claims are also directed to a method of treating "a cancer regulated by HER-kinase axis activation that is resistant to therapeutic treatments directed exclusively at either the PPAR-gamma pathway or the HER-kinase axis." While ciglitazone and rosiglitazone are PPAR-gamma agonists, they are not NSAIDs. Further, Mitsiades *et al.* does not teach the treatment of a resistant cancer. Consequently, even if it would have been obvious to one of skill in the art to optimize the effectiveness of the treatment, which Applicants in no way conced, Mitsiades *et al.* still does not teach each and every element of the claims and thus, does cannot render these claims obvious.

In light of the above remarks, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

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All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If for any reason Examiner finds the application other than in condition for allowance, Examiner is requested to call either of the undersigned attorneys at the Los Angeles telephone number (213) 633-6800 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,
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Attachments: Exhibits A and B.

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